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Reduced-Intensity Allogeneic Stem Cell Transplantation in Adults and Children with Malignant and Nonmalignant Diseases: End of the Beginning and Future Challenges

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ABSTRACT

During the last 10 years, multiple studies using reduced-intensity (RI) conditioning followed by allogeneic stem cell transplantation (AlloSCT) have been reported in adult and, less so, pediatric recipients. RI AlloSCT allegedly eradicates malignant cells through a graft-versus-leukemia/graft-versus-tumor effect provided by alloreactive donor T lymphocytes, natural killer cells, or both. Various studies have clearly demonstrated a graft-versus-leukemia/graft-versus-tumor effect in hematologic malignancies and solid tumors. Acute short-term toxicity, including infection and organ decompensation after myeloablative conditioning therapy, can result in a significant incidence of early transplant-related mortality. More importantly, long-term late effects—including growth retardation, infertility, and secondary malignancies—are major complications after myeloablative conditioning therapy, especially in vulnerable children, who are more susceptible to these complications. Recent results comparing RI conditioning with myeloablative conditioning followed by HLA-matched sibling AlloSCT have demonstrated a significant reduction in use of blood products, risk of infections, transplant-related mortality, length of hospitalization, and feasibility of conditioning therapy in outpatient settings. Despite the success of RI AlloSCT, large prospective randomized multicenter studies are necessary to define the appropriate patient population, optimal conditioning regimens and pretransplantation immunosuppression, role of donor lymphocyte infusions, duration of hospitalization, overall survival, cost-benefit ratio, and differences in long-term effects to evaluate the role of RI AlloSCT more fully. We review the recent experience of RI AlloSCT in adults and children with both malignant and nonmalignant diseases and discuss the challenges for the future.

KEY WORDS

Reduced-intensity stem cell transplantation • Nonmyeloablative transplantation • GVL • GVHD

INTRODUCTION

Allogeneic hematopoietic stem cell transplant (AlloSCT) from related or unrelated histocompatible donors has been well established as potentially curative therapy for children and adults with selected hematologic malignancies [1]. The concept of AlloSCT as a treatment option for hematologic malignancies has long been based on the assumption that myeloablative doses of cytotoxic therapy were required for both disease eradication and host immunosuppression. Several observations, however, have challenged the dogma that high-dose cytotoxic therapy was a sine qua non for disease eradication with AlloSCT. These observations include (1) decreased relapse rates in recipients of AlloSCT compared with autologous or syngeneic stem cell transplants (SCT) [2]; (2) increased risk of relapse after T cell–depleted compared with unmodified allografts [3]; (3) decreased risk of relapse in patients who develop acute or chronic graft-versus-host disease (GVHD) after allografting [4-10]; and (4)

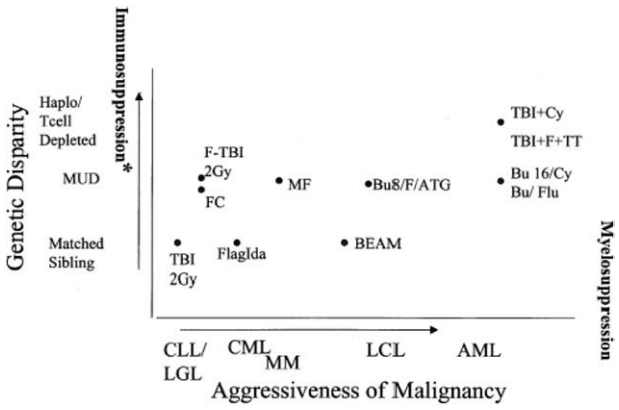

Figure 1. The most widely used preparative regimens in nonmyeloablative stem cell transplantation and conventional transplantations. The aggressiveness of the underlying malignancy and the donor-recipient genetic disparity, the recipient's immunocompetence, and sensitization are important in the decision-making process for each clinical situation. MUD indicates matched unrelated donor; CLL/LGL, chronic lymphocytic leukemia/low-grade lymphoma; CML, chronic myelogenous leukemia; LCL, large-cell lymphoma; AML, acute myelogenous leukemia; MM, multiple myeloma; F-TBI 2 Gy, fludarabine and total body irradiation (TBI) 2 Gy; FlagIda, fludarabine, cytosine arabinoside, and idarubicin; MF, melphalan and fludarabine; BEAM, carmustine, etoposide, cytosine arabinoside, and melphalan; Bu8/F/ATG, busulfan 8 mg/m^2, fludarabine, and antithymocyte globulin; TBI+Cy, TBI and cyclophosphamide; TBI+F+TT, TBI, fludarabine, and thiotepa; Bu 16/Cy, busulfan 16 mg/m^2 and cyclophosphamide; Bu/Flu, busulfan (escalated doses) and fludarabine. *The immunosuppression required depends on the genetic disparity, immunocompetence, and sensitization of the recipient. Reprinted with permission from Elsevier Ireland Ltd [17].

remission induction after donor lymphocyte infusion (DLI) in some patients whose disease had relapsed after SCT [11-16]. Taken together, these observations suggested that immune cell genetic disparities between donors and recipients also included graft-versus-tumor (GVT) effects capable of eradicating the underlying host malignancy. These observations, in addition to better ways of controlling both host and donor immune reactions, led to reassessment of strategies for AlloSCT. Specifically, instead of eradicating tumors through intensive and, thereby, toxic chemoradiation, the SCT donor's immune cells might be used for that purpose, relying on allogeneic GVT effects. Elimination of high-dose cytotoxic therapy would then allow elderly or medically infirm patients to be treated with SCT.

There is a substantial heterogeneity between various reduced-intensity (RI) conditioning regimens in terms of dose of chemotherapy and radiotherapy and degree of immunosuppression [17] (Figure 1). As a working definition, a truly nonmyeloablative regimen should not eradicate host hematopoiesis and should allow relatively prompt hematopoietic recovery (<28 days) without a transplantation [18]. Upon engraftment, mixed chimerism should be present. If the graft is rejected, prompt autologous recovery should occur. Conversely, an ablative regimen requires hematopoietic transplantation for recovery, and complete chimerism occurs upon engraftment. Many of the reduced-toxicity regimens referred to as nonmyeloablative have not been documented to meet these criteria [19]. These regimens require a transplantation for hematologic recovery, and if the graft is rejected, prolonged aplasia typically occurs. These should be referred to as "reduced-toxicity" ablative regimens [20]. This distinction in intensity of regimens is crucial to differentiate the graft-versus-leukemia (GVL) effects of donor engraftment from the antitumor effect of the conditioning regimen.

The theoretical reduction in incidence of acute GVHD after RI AlloSCT may be due to limited tissue damage in the recipient. This may translate into decreased cytokine storm, which has been described after myeloablative conditioning therapy to provide a proinflammatory milieu for the development of acute GVHD [21,22]. Also, studies in animals have demonstrated that the development of transient mixed donor-host chimerism may facilitate establishment of mutual tolerance, which, in turn, may downregulate graft-versus-host (GVH) activity [23,24]. Several years ago, Storb et al. [25] and Georges et al. [26] originally demonstrated the ability to achieve mixed and, ultimately, complete donor chimerism after RI conditioning (200 cGy) in dog leukocyte antigen–identical canine allogeneic transplant recipients and subsequently demonstrated the successful ability to administer DLI as potential adoptive cellular immunotherapy after RI conditioning in a similar animal model. Subsequently, the group from Israel [27] demonstrated the initial early results of this approach in humans with refractory hematologic malignancies with comorbid features. In this article, we review the recent experience of RI AlloSCT in adults and children with both malignant and nonmalignant diseases and discuss the challenges for the future.

RI AlloSCT FOR ADULT ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME

The median age of presentation in acute myeloid leukemia (AML) is more than 60 years, and the adequate management of AML in older patients remains the major challenge. Because of an increase in comorbidities such as infections and impaired organ function, the arbitrary age limit for intensive conditioning therapy before allogeneic transplantation in patients with AML is between 50 and 55 years. RI AlloSCT might be one way to reduce the substantial treatment-related mortality of older patients and thus provide the curative potential of allogeneic cell therapy. How-

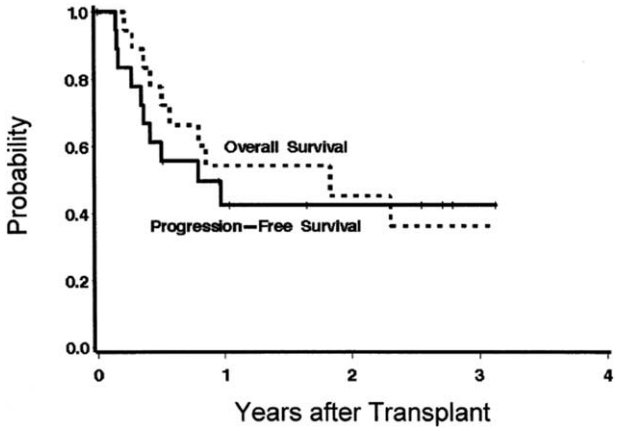

Figure 2. Kaplan-Meier survival estimates of overall and progression-free survival for 18 patients with de novo or secondary AML in CR1 after nonmyeloablative SCT (2 Gy of total body irradiation with or without 90 mg/m^2 of fludarabine). Reprinted with permission from Blackwell Publishing [30].

ever, older patients with refractory or relapsed AML who receive nonmyeloablative SCT seem to have rapid recurrence and poor long-term survival. This may be because the GVL effect is less potent or because the disease progresses too rapidly [28]. Similarly, patients with myelodysplastic syndrome (MDS) and secondary AML were reported to have poor disease-free survival [29]. A certain amount of cytoreduction may be necessary for patients with MDS or relapsed or refractory AML. However, elderly medically infirm patients with AML in first complete remission (CR1) who received a nonmyeloablative SCT from matched sibling donors seem to have survival comparable to that with myeloablative SCT [30] (Figure 2).

Should an RI AlloSCT approach be extended routinely to younger adults with AML in CR1 otherwise eligible for conventional myeloablative SCT? Gorin et al. [27] have demonstrated CR rates of 50% after RI AlloSCT in a younger cohort of patients with AML. In most of the studies mentioned in Table 1, the number of patients enrolled in the studies was small, stem cell donors were different, conditioning regimens and pretransplantation and posttransplantation immunosuppression were variable, many of the studies were single-center studies, and, most importantly, follow-up was short. With all of these issues, it is difficult to compare various studies, and the results should be interpreted cautiously. There is a need for multi-institutional randomized trials to compare various factors that influence the outcome of RI AlloSCT. In the future, the role of consolidation with gemtuzumab ozogamicin after RI AlloSCT to eradicate minimal residual disease should also be studied. Is there any role for tailoring conditioning regimens (truly nonmyeloablative versus RI) according to cytogenetics, gene-expression profiling, or the proteomics of AML? Furthermore, routine molecular monitoring of *WT1* gene transcripts might be helpful for the prediction and management of relapse after RI AlloSCT. Results from various studies [27-34] are summarized in Table 1.

RI AlloSCT FOR ADULT CHRONIC MYELOID LEUKEMIA

Although myeloablative allogeneic transplantation is a curative therapy for chronic myeloid leukemia (CML), treatment-related mortality is still a major cause of posttransplantation death, especially for patients older than 40 years. The rate of CR in response to DLI has been impressive, with 70% to 80% of relapsed CML patients achieving durable remissions after DLI [10,12,35-38]. Given the therapeutic role of DLI in patients with CML and considering the documented therapeutic potential of alloreactive donor lymphocytes administered after bone marrow transplantation in CML, it seems reasonable to exploit the therapeutic use of alloreactive donor lymphocytes after establishment of host-to-graft transplantation tolerance induced by engraftment of donor stem cells after RI conditioning. Because CML in chronic phase is a rather indolent disease, it seems to be an ideal disease to evaluate the RI AlloSCT approach. Patients with CML receiving RI AlloSCT in first chronic phase have very good overall survival (OS) and disease-free survival [39,40] (Figure 3). However, patients receiving RI AlloSCT in blast crisis seem to have a poor prognosis, which is also the case for conventional myeloablative AlloSCT. Patients with CML in blast crisis might benefit from cytoreduction before RI AlloSCT.

The field of CML therapy continues to change, and the question of to whom to apply the nonmyeloablative approach is problematic. Restricting the therapy to only those patients who experience treatment failure with imatinib or those who have a related or unrelated donor but are too old or too ill for conventional transplantation would confine the treatment to a very small group of patients. One possible approach might be to add nonmyeloablative transplantations as an immunologic adjuvant after initial cytoreduction with imatinib, followed by the addition of imatinib after transplantation to eradicate any residual disease. Larger studies are required to evaluate the role of RI AlloSCT in CML. Results from other studies [31,41-44] are included in Table 2.

RI AlloSCT FOR CHRONIC LYMPHOID LEUKEMIA

Most patients with chronic lymphoid leukemia (CLL) present in advanced age, and the relatively indolent course of the disease in a substantial propor-

Table 1. *RI AlloSCT for Adult Patients with AML/MDS*

Study	n	Disease/Status†	Median Age, y (Range)	Donor	Regimen	Acute GVHD Prophylaxis	Myeloid and Platelet Recovery (Median Day)	Donor Chimerism* (% Patients)	Incidence of GVHD		Outcome
									Acute	Chronic	
Gorin [27]	40	AML (32)/MDS (8) CR1–12, CR2–8, RR-12 RAEB-8	NA (3–64)	MUD MRD	Bu/Flu/ATG or Flu/low-dose TBI	CSP	NA	100	47%	NS	CR-50%
Giralt [28]	31	AML (31) 1st CR-8 >1st CR-23	61 (21–74)	MRD MMRD	Flu/Ara-C/Ida Ara-C/CDA	CSP/tacrolimus ± steroids ± MTX	13/17	65	19%	NA	1-y OS-47% 1-y DFS-34%
Kroger [29]	37	AML (7) MDS (30) RA-5 RAEB-6 RAEBT-11 CMML-3 sRA-3 sRAEBT-2 sAML-7	55 (23–72)	MUD MRD	Flu/Bu/ATG	CSP and MTX	14/14	80	37%	48%	DFS-12%
Feinstein [30]	18	AML (18) 1st CR	59 (36–73)	MSD	Low-dose TBI or Flu/low-dose TBI	CSP/MMF	4/0	80	45%	22%	1-y OS-54% 1-y PFS-42%
Giralt [31]	43	AML (43) 1st CR-1 >1st CR-5 RR-27 UR-10	52 (43–60)	MRD MMRD MUD	Flu/Mel Cladribine/Mel	Tacrolimus and MTX	14/21	100	39%	45%	2-y DFS-34%
Rezvani [32]	149	MDS (53) PR/CR-23 AML (64) CR1 and 2–23, >CR2–41 ALL (36) 9 CR1, 10 CR2, 14 PR	51 (3–68)	MSD MUD	Flu-based	CSP and MTX	NA	77	43%	NA	OS-35%
Corradini [33]	12	AML (5)/MDS (6) ALL (1) CR1–3, ≥CR2–2, UR-4 RR-3	49 (20–68)	MSD	Flu/Thio/Cy	CSP and MTX	13/15	88	45%	47.5%	CR-75%
McSweeney [34]	13	AML (12)-CR1–6, CR >1–2 Induction failure-3 MDS-RAEBT-1 ALL(1)-CR3	60 (36–72)	MSD	Low-dose TBI	CSP/MMF	11/11	92	47%	74%	CR-45%

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; CR, complete remission; RR, refractory relapse; RAEB, refractory anemia with excess blasts; RAEBT, refractory anemia in blast transformation; ALL, acute lymphoblastic leukemia; RA, refractory anemia; CMML, chronic myelomonocytic leukemia; sRA, secondary refractory anemia; sRAEBT, secondary refractory anemia in blast transformation; sAML, secondary AML; UR, untreated relapse; PR, partial remission; MUD, matched unrelated donors; MRD, matched related donors; MMRD, mismatched related donors; MSD, matched sibling donors; Bu, busulfan; Flu, fludarabine; ATG, antithymocyte globulin; TBI, total body irradiation; Ara-C, cytosine arabinoside; Ida, idarubicin; CDA, cladribine; Mel, melphalan; Thio, thiotepa; Cy, cyclophosphamide; CSP, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; NS, not stated; myeloid recovery, absolute neutrophil count >500/μL; platelet recovery, >20 000/μL; NA, not available; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

*Any degree of donor chimerism.

†Number in parentheses represents number of patients with each discharge subtype.

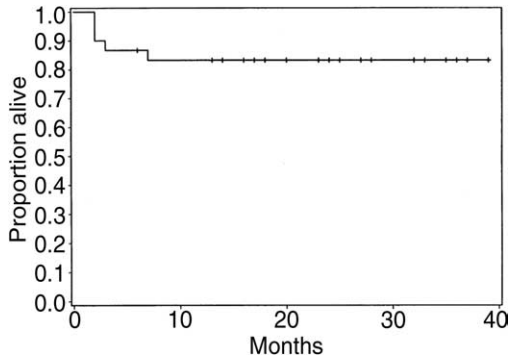

Figure 3. Kaplan-Meier survival estimates for 30 patients with CML conditioned with low-dose single-exposure total body irradiation. Reprinted with permission from the American Society for Blood and Marrow Transplantation [40].

tion of cases makes symptom palliation a reasonable treatment goal in many cases. Nevertheless, approximately one third of the patients are younger than 60 years old, and 10% to 15% are younger than 50 years. In this group of patients, the aim of treatment cannot merely be palliative. Young patients with poor-risk CLL requiring therapy should be offered experimental therapies aimed at achieving cure. The benefit of allogeneic transplantation is potentially related to GVL effects, and prolonged remissions have been reported in patients with advanced CLL receiving high-dose chemotherapy and allogeneic bone marrow or peripheral blood stem cell (PBSC) transplantation [45]. However, high-dose myeloablative AlloSCT is associated with substantial transplant-related mortality (TRM) (31% at 3 months; International Bone Marrow Transplantation Registry) [46]. A European Bone Marrow Transplant Registry study comparing RI AlloSCT with conventional AlloSCT for CLL has suggested that outcomes may be superior with an RI approach, and in this series, the cumulative TRM was 18% [47]. In a comparison of ablative versus nonablative transplantations at M.D. Anderson Cancer Center, the long-term survival seems to be similar (approximately 40%) despite the higher age range of nonablative SCT patients who are minimal residual disease negative and have longer disease-free intervals with improved OS than patients who remain minimal residual disease positive [48] (Table 2). Recently, Khouri et al. [45] demonstrated GVL activity after RI AlloSCT in patients with persistent or progressive disease by early taper and discontinuation of tacrolimus followed by rituximab and DLI in patients who did not develop GVHD. However, immunomanipulation was associated with a high incidence of GVHD (60% chronic). Moreover, the natural history of response to fludarabine, cyclophosphamide, and rituximab without allograft in CLL was not described in the study [45].

As yet, long-term follow-up information on RI AlloSCT in CLL is limited. The role of RI AlloSCT needs to be clearly defined for CLL patients. Patients who do not attain a CR with initial therapy or who have high-risk genetic abnormalities (ie, del[11q22-q23], del[17p13], unmutated somatic V_H gene status, and p53 mutations) should be considered candidates for RI AlloSCT in well-designed clinical trials. The role of rituximab and alemtuzumab in RI conditioning regimens for CLL needs to be studied further. Results from other studies in CLL [45,49,50] are included in Table 2.

RI AlloSCT FOR MULTIPLE MYELOMA

Autologous SCT after high-dose myeloablative therapy has increased CR rates to 50% in patients newly diagnosed with myeloma, thus resulting in a significant increase in event-free survival and OS compared with conventional therapy [51-53]. Although a substantial fraction of patients remain alive and disease free for more than 10 years, the frequency of disease progression or relapse continues to be high after transplantation, especially in patients with poor prognostic features at presentation [52,54]. Although myeloablative AlloSCT uses a stem cell source that is not contaminated with myeloma cells and induces a graft-versus-myeloma effect [55], the survival rates have been inferior to those after myeloablative autologous SCT because of high TRM [56-58]. However, AlloSCT is possibly the only genuinely curative therapy in multiple myeloma (MM). The RI AlloSCT approach is associated with less TRM while harnessing the GVT effect. A nonmyeloablative conditioning regimen with melphalan 100 mg/m^2 combined with DLIs has induced good disease control at 1 year but with a significant rate of GVHD in 31 patients with high-risk MM [59] (Figure 4). Because early TRM is reduced with a nonmyeloablative conditioning regimen, this approach should be tested in frontline treatment in older patients. However, preliminary RI AlloSCT studies in MM have clearly shown that results are related to disease status, and the relapse rates are high in patients with advanced disease. Therefore, reducing tumor burden with autologous SCT before RI AlloSCT should be considered. The Seattle group has reported results with autologous SCT followed by nonmyeloablative AlloSCT in 44 patients [60]. Although GVHD remains a problem, the feasibility of this approach has been demonstrated. Kroger et al. [61] reported significantly less transplant-related organ toxicity and an overall response rate of 90% after RI AlloSCT in MM patients who received allografts from matched unrelated donors. Results from most of the studies are encouraging, but because the studies are small, mostly single-center studies and because follow-up is still short, results should be cautiously

Table 2. *R1 AlloSCT in Adults with Chronic Myeloid and Chronic Lymphocytic Leukemia*

Study	n	Disease/Status	Median Age, y (Range)	Donor	Regimen	Acute GVHD Prophylaxis	Myeloid and Platelet Recovery (Median Day)	Donor Chimerism* (% Patients)	Incidence of GVHD		Outcome
									Acute	Chronic	
Giralt [31]	27	CML 1st CP-6 Blast phase-21	52 (43–60)	MRD MMRD MUD	Flu/Mel	Tacrolimus and MTX	14/21	100	39%	45%	1-y OS-32% 1-y DFS-34%
Or [39]	24	CML-1st CP	35 (3–63)	MRD MUD	Bu/Flu Bu/Flu/ATG	CSP/MTX	16/3	100	75%	55%	5-y OS-85% DFS-85%
Khoury [40]	30	CML-1st CP-28 Blast phase-2	47 (21–63)	MSD	Cy/low-dose TBI	CSP	11/14	95	90%	92%	2-y OS-83%
Ehninger [41]	45	CML-1st CP-20 ≥1st CP-25	52 (25–65)	MRD MUD	Bu/Flu	CSP ± MMF ± MTX and steroids	14/17	74	65%	NA	1-y OS-62% 1-y DFS-34%
Bornhauser [42]	44	CML 1st CP-26 AP-11 BC-7	52 (25–65)	MRD MUD	Bu/Flu	CSP CSP + MMF CSP + MTX	8/5	99	61%	NA	DFS-41%
Barta [43]	36	CML 1st CP-26 AP-10	49 (15–59)	MSD MMSD	Ara-C/dibromomannitol	CSP + MTX	15/29	94	25%	69%	OS-83% DFS-77%
Raiola [44]	15	CML 1st CP-9 AP-6 BC-2	52 (43–60)	MSD	Thio/Cy/ATG	CSP + MTX	17/20	79	51%	45%	OS-80%
Khouri [45]	17	CLL-1st relapse (CS)-8 >1st relapse (CRef)-7 Primary refractory-2	54 (43.6–73)	MSD	Flu/Cy Flu/Cy/rituximab	Tacrolimus and MTX	10/NA	100	41%	60%	PFS-60%
Schetelig [49]	30	CLL PR/CR (CS)-15 SD/PD (CRef)-15	NA	MSD MUD	Bu/Flu/ATG	CSP + MMF CSP + MTX	18/15	NA	50%	NA	2-y OS-79% 2-y PFS-61%
Dreger [50]	77	CLL CR-8 PR-42 <PR-27	54 (30–66)	MSD MUD	Low-dose TBI Low-dose TBI/Flu Flu/alkylator ± ATG ± alemtuzumab	CSP CSP + MMF CSP + MTX	12/NA	87			OS-72% EFS-56%

CML indicates chronic myeloid leukemia; CP, chronic phase; AP, accelerated phase; BC, blast crisis; CLL, chronic lymphocytic leukemia; CS, chemosensitive; CRef, chemorefractory; PR, partial remission; CR, complete remission; SD, stable disease; PD, progressive disease; NA, not available; MRD, matched related donors; MMRD, mismatched related donors; MUD, matched unrelated donors; MSD, matched sibling donors; MMSD, mismatched sibling donors; Flu, fludarabine; NA, not available; Mel, melphalan; Bu, busulfan; ATG, antithymocyte globulin; TBI, total body irradiation; Ara-C, cytosine arabinoside; Thio, thiotepa; Cy, cyclophosphamide; MTX, methotrexate; CSP, cyclosporine; MMF, mycophenolate mofetil; myeloid recovery, absolute neutrophil count >500/μL; platelet recovery, >20 000/μL; OS, overall survival; DFS, disease-free survival; EFS, event-free survival; PFS, progression-free survival.

*Any degree of donor chimerism.

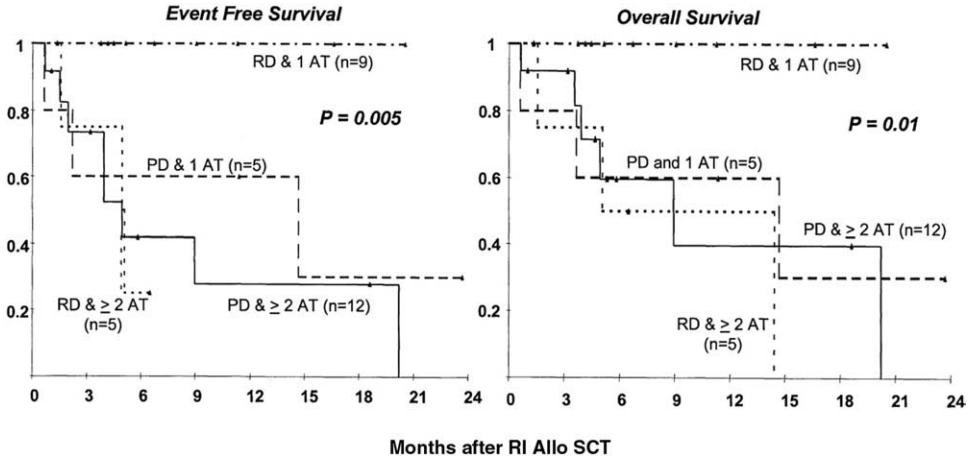

Figure 4. Kaplan-Meier estimate of actuarial survival after allografts according to the number of prior myeloablative autologous SCTs and disease status. Patients with responsive disease (RD; including CR and partial response) receiving 1 myeloablative autologous SCT before RI AlloSCT had significantly better event-free survival and OS compared with patients with progressive disease (PD) and/or ≥2 myeloablative autologous SCTs. Reprinted with permission from the American Society of Clinical Oncology [59]. AT indicates autologous SCT.

interpreted, as late relapses are common in MM. Ongoing multicenter studies are using genetic randomization to compare RI AlloSCT and a second autologous SCT in patients who have received a first autologous SCT. Also, randomized studies should be performed to compare RI AlloSCT with conventional myeloablative AlloSCT. As the field of MM therapy continues to advance, the role of thalidomide, proteasome inhibitors, antisense bcl-2, and idiotype dendritic cell vaccination should be studied before or after RI AlloSCT. Results from other studies in MM [61-66] are included in Table 3.

RI AlloSCT FOR ADULT LYMPHOMA

AlloSCT theoretically provides several advantages over autologous SCT, including provision of a lymphoma-free graft, reduced rates of secondary MDS and leukemia, and a potentially curative graft-versus-lymphoma effect. Increasing evidence has accumulated to support the concept of a therapeutically relevant graft-versus-lymphoma effect for a number of lymphoma subtypes, and a gradual improvement in TRM rates has made these approaches more attractive. RI approaches allow application to a broader patient group, but follow-up in these studies is limited. In lymphoma, histology, chemosensitivity, and prior transplantation are important prognostic factors after RI AlloSCT. Results for nonmyeloablative AlloSCT are particularly promising in low-grade non-Hodgkin lymphoma (NHL), and the graft-versus-lymphoma effect may augment response and delay or prevent relapse [67,68]. However, for aggressive disease, nonmyeloablative regimens should be indicated only for patients with minimal disease, because the nonmyeloablative regimens are unable to control the tumor before the generation of a graft-versus-lymphoma effect and/or lack the ability to control rapidly proliferating disease [69]. Patients with aggressive disease may require a higher-dose regimen.

The role of RI AlloSCT in NHL is compromised by the paucity of large clinical trials. There are no randomized clinical trials of RI AlloSCT versus conventional myeloablative AlloSCT or autologous SCT. Most reports include highly heterogeneous patient cohorts with varying histologies (low-, intermediate- and high-grade NHL, as well as Hodgkin disease) and varying stages of disease (from patients in first CR to those in chemorefractory late relapse). The relative merits of more or less intensive preparative regimens for various histologies of NHL and of strategies that incorporate T-cell depletion need to be more clearly defined by more widespread collaborative studies. There is also a need to define the role of monoclonal antibodies and radioimmunotherapy in the conditioning regimens in RI AlloSCT. Results from various studies in NHL [67-75] are included in Table 4.

UNRELATED RI AlloSCT FOR OTHER HEMATOLOGIC MALIGNANCIES

There are only a few studies evaluating unrelated RI AlloSCT for hematologic malignancies. Maris et al. [76] demonstrated that matched unrelated adult donor AlloSCT after RI conditioning for other hematologic malignancies was feasible in patients ineligible for conventional AlloSCT. PBSC RI AlloSCT conferred higher donor T-cell chimerism, greater durable engraftment, and better progression-free and OS compared with marrow RI AlloSCT. The incidence of GVHD (52%) and the 1-year OS rate (52%) were comparable to those with related RI AlloSCT. Re-

Table 3. *RI AlloSCT in Adults with Multiple Myeloma*

Study	n	Disease Status	Median Age, y (Range)	Donor	Regimen	Acute GVHD Prophylaxis	Myeloid and Platelet Recovery (Median Day)	Donor Chimerism* (% Patients)	Incidence of GVHD		Outcome
									Acute	Chronic	
Badros [59]	31	PD-17 NCR-6 PR-5 CR2–3	56 (38–69)	MSD MUD	Mel Flu/Mel/TBI	CSP CSP + steroids	14/15	89	58%	33%	1-y OS-71%
Maloney [60]	44	CR-6 PR-22 UR-7 Ref-19	52 (29–71)	MSD	Low-dose TBI Flu/low-dose TBI	CSP + MMF	0/0	100	38%	56%	ORR-81%
Kroger [61]	21	PR-1 MR-1 NC-3 PD-8	50 (32–61)	MUD	Flu/Mel/ATG	CSP + MMF CSP + MTX	16/22	100	57%	37%	ORR-90% 2-y EFS-74%
Lee [62]	45	≥PR-14 <PR-34	52 (38–68)	MSD MUD	Mel Mel/low-dose TBI/Flu	CSP CSP + steroids	12/23	93	78%	58%	3-y OS-36%
Peggs [63]	20	CR-1 PR-18 MR-1	47 (34–58)	MRD MUD MMUD	Flu/Mel/alemtuzumab	CSP	45/52	95	155	10%	2-y OS-71%
Kroger [64]	17	PR-12 MR-3 NC-2	51 (32–64)	MMRD MUD	Flu/Mel/ATG	CSP + MTX	16/23	100	38%	40%	CR-73%
Giralt [65]	22	RR-8 SR-8 Pref-2 CR-1	51 (45–64)	MSD MUD	Flu/Mel	Tacrolimus and MTX	12/14	80	72%	27%	RR-72% 2-y PFS-19%
Mohty [66]	41	PR-29 CR-1 PD-11	52 (35–61)	MSD	Bu/Flu/ATG	CSP CSP + MTX	17/10	NA	43%	41%	2-y OS-62% 2-y PFS-41%

PD indicates progressive disease; NCR, near-complete remission; PR, partial remission; CR, complete remission; UR, untreated relapse; Ref, refractory disease; MR, minimal response; NC, no change; RR, response rate; SR, chemosensitive relapse; Pref, primary refractory; MSD, matched sibling donors; MUD, matched unrelated donors; MRD, matched related donors; MMUD, mismatched unrelated donors; MMRD, mismatched related donors; Mel, melphalan; Flu, fludarabine; TBI, total body irradiation; ATG, antithymocyte globulin; Bu, busulfan; CSP, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; myeloid recovery, absolute neutrophil count >500/μL, platelet recovery, >20 000/μL; NA, not available; OS, overall survival; ORR, overall response rate; EFS, event-free survival; RR, refractory relapse; PFS, progression-free survival.

*Any degree of donor chimerism.

Table 4. *R1 AlloSCT in Adults with Lymphoma*

Study	n	Disease	Disease Status	Median Age, y (Range)	Donor	Regimen	Acute GVHD Prophylaxis	Myeloid and Platelet Recovery (Median Day)	Donor Chimerism* (% Patients)	Incidence of GVHD		Outcome
										Acute	Chronic	
Khouri [67]	10	Low-grade lymphoma	SR-8 SD-2	50 (36–60)	MSD	Flu/Cy	Tacrolimus + MTX	11/NA	80	10%	10%	16-mo PFS and OS-100%
Khouri [68]	20	Indolent NHL	≥CR2–12 PR-6 PD-2	51 (31–68)	MSD	Flu/Cy ± rituximab	Tacrolimus + MTX	11/NA	80	20%	64%	CR-100%
Khouri [69]	15	Aggressive lymphoma	RR-6 PR-6	55 (31–64)	MSD	Flu/Ara-C/cisplatin	Tacrolimus + MTX	NA	86	13%	NS	1-y OS-60% 1-y PFS-40%
Faulkner [70]	65	Low- and high-grade NHL, MCL, PTCL	Good risk-13, intermediate risk-17, poor risk-27, unknown-8	45 (19–60)	MSD MMSD MUD	BEAM/alemtuzumab	CSP + MTX	15/15	63	26%	17%	2-y OS-68% 2-y EFS-58%
Carella [71]	15	NHL HD	PR-6 1st relapse-2 >1st relapse-6 PR-1	36 (22–60)	MSD	Flu/Cy	CSP + MTX	10/15	100	60%	13%	CR-84%
Khouri [72]	18	MCL	CR-8 PR-8 SD-2	56 (46–64)	MSD MMSD MUD	Flu/Cy/rituximab Flu/Ara-C/cisplatin	Tacrolimus + MTX	11/10.5	100	17%	36%	CR-94% 3-y EFS-82%
Bishop [73]	15	Refractory NHL	RR-10 Pri Ref-3 UR-1 SR-1	49 (33–63)	MSD MMSD	Flu/Cy	CSP	9/10	100	71%	54%	CR-60% OS-57%
Anderlini [74]	6	Advanced HD	RR-3 SR-3	29 (22–30)	MSD MUD	Flu based	CSP or tacrolimus ± MTX	13/0	80	66%	50%	CR-50%
Corradini [75]	17	PTCL	UR-1 PD-2 ≥CR2–2 ≥PR2–12	41 (23–60)	MSD MMSD MUD	Flu/Cy/thiotepa	CSP + MTX	14/17	53	35%	50%	3-y OS-81% 3-y PFS-64%

NHL indicates non-Hodgkin lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma; HD, Hodgkin disease; SR, sensitive relapse; SD, stable disease; CR, complete remission; PR, partial remission; PD, progressive disease; RR, refractory relapse; Pri Ref, primary refractory disease; UR, untreated relapse; MSD, matched sibling donors; MMSD, mismatched sibling donors; MUD, matched unrelated donors; Flu, fludarabine; Cy, cyclophosphamide; Ara-C, cytosine arabinoside; BEAM, carmustine, etoposide, cytarabine, and melphalan; MTX, methotrexate; CSP, cyclosporine; myeloid recovery, absolute neutrophil count >500/μL; platelet recovery, >20 000/μL; NA, not available; NS, not stated; PFS, progression-free survival; OS, overall survival; EFS, event-free survival.

*Any degree of donor chimerism.

cently, Sorror at al. [77] reported a retrospective analysis of patients with various hematologic malignancies, comparing severe toxicities and 1-year nonrelapse mortality after unrelated SCT after either nonablative or ablative conditioning regimens. Even though nonablative patients had significantly higher pretransplantation comorbidity scores and were older, they experienced fewer grade III to IV toxicities than ablative patients. Furthermore, the incidence of grade III to IV acute GVHD was significantly lower in nonablative patients. The 1-year nonrelapse mortality rate was 20% in nonablative patients compared with 32% in ablative patients. There is a need for large clinical studies comparing unrelated RI AlloSCT with unrelated myeloablative AlloSCT for various hematologic and nonhematologic diseases and solid tumors.

RI AlloSCT FOR ADULT SOLID TUMORS

The potential of immune GVT effects to control advanced solid tumors is documented in a nonallogeneic setting. Several findings justify AlloSCT for solid tumors because GVT effects can target tissue-specific polymorphic antigens that are not derived from hematopoietic lineages. Some solid tumors are sensitive to immunotherapy, such as renal cell carcinoma (RCC), melanoma, and ovarian cancer, and in theory, all carcinomas arising from epithelial tissues that are targets of acute and chronic GVHD should be susceptible to a GVT effect [78]. RI conditioning regimens may provide a platform for antigen-specific immunotherapy directed against relevant tumor-associated antigens. In a landmark article, Childs et al. [79] reported regression of metastatic RCC after nonmyeloablative allogeneic PBSC transplantation, with compelling evidence that regression of metastatic RCC was mediated by a GVT effect (Table 5). Recently, Bishop et al. [80] reported on 16 patients with progressive metastatic breast cancer who were conditioned with cyclophosphamide and fludarabine before RI AlloSCT. Six patients had tumor regression at a time that was remote from the potential antitumor effects of cytotoxic chemotherapy in the transplantation conditioning regimen. These results suggest that tumor regression was associated with an immune-mediated reaction related to AlloSCT. Results of nonmyeloablative SCT in patients with metastatic melanoma have thus far been disappointing. In an analysis of 25 patients with metastatic melanoma undergoing nonmyeloablative SCT at 4 transplant centers, the median survival was only 100 days, and rapid disease progression was the major cause of death [81].

RI AlloSCT has been performed in patients with various other solid tumors, and responses have been observed in a minority of patients; moreover, these responses are partial and of relatively short duration

Table 5. *RI AlloSCT for Adults with Solid Tumors*

Study	n	Disease	Disease Status	Median Age, y (Range)	Donor	Regimen	Acute GVHD Prophylaxis	Myeloid and Platelet Recovery (Median Day)	Donor Chimerism* (% Patients)	Incidence of GVHD		Outcome
										Acute	Chronic	
Childs [79]	19	Metastatic RCC	PD-19	48 (37–65)	MSD MMSD	Flu/Cy	CSP	10.5/8	100	53%	21%	ORR-55%
Bishop [80]	16	Metastatic BC	PD-16	43 (32–56)	MSD	Flu/Cy	CSP	10/14	100	62%	30%	PR-37%
Blaise [83]	57	RCC and BC, malignant melanoma	PD-39 SD-18	45 (35–55)	MSD	Flu/Bu/ATG	CSP	15/13	90	65%	59%	ORR-14%
Rini [84]	15	Metastatic RCC	PD-15	54 (47–61)	MSD	Flu/Cy	Tacrolimus + MMF	12/8	41	17%	50%	PR-33%
Bregni [85]	13	RCC and BC	PD-9 SD-4	44 (18–60)	MSD	Flu/Cy Flu/Cy/Thio	CSP + MTX	12/12	90	61%	53%	ORR-46%
Makimoto [86]	14	Solid tumors	PD-14	23 (4–56)	MRD MMRD	Flu/Bu	CSP CSP + MTX	11/12	92	28%	14%	PR-7%
Ueno [87]	23	RCC and BC	PD-23	44.5 (36–53)	MSD MUD	Flu/Mel	Tacrolimus + MTX	12/17.5	100	39%	43%	ORR-45%

RCC indicates renal cell carcinoma; BC, breast carcinoma; PD, progressive disease; SD, stable disease; MSD, matched sibling donors; MMSD, mismatched sibling donors; MRD, matched related donors; MMRD, mismatched related donors; MUD, matched unrelated donors; Flu, fludarabine; Cy, cyclophosphamide; Bu, busulfan; ATG, antithymocyte globulin; Thio, thiotepa; Mel, melphalan; CSP, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; myeloid recovery, absolute neutrophil count >500/μL; platelet recovery, >20 000/μL; ORR, overall response rate; PR, partial response.
*Any degree of donor chimerism.

because of the rapid growth of these tumors and the delay in occurrence of a GVT effect. Whether GVT effects might be more effective in patients with minimal residual disease, such as after autologous transplantation or aggressive surgical debulking, should be explored. RI AlloSCT might be beneficial to the patients who have slow-growing solid tumors. Recently, Igarashi et al. [82] demonstrated enhanced susceptibility of RCC and melanoma cells to natural killer (NK) cells with killer immunoglobulin receptor incompatibility; this suggests that the NK cell–mediated antitumor effects seen against AML after killer immunoglobulin receptor–incompatible mismatched allogeneic transplantation might be induced in a similar fashion against selected solid tumors. Results from other solid-tumor studies [83-87] are included in Table 5.

RI AlloSCT FOR AUTOIMMUNE DISORDERS

Animal models of autoimmune disease, such as systemic lupus erythematosus and rheumatoid arthritis, have shown that AlloSCT may be superior to autologous SCT, with higher cure rates and protection from disease progression, relapse, or both [88-91]. The rationale for investigating AlloSCT for medically refractory autoimmune diseases includes in part the following: (1) elimination or suppression of autoreactive clones, (2) elimination or suppression of maternal-fetal microchimerism, (3) amelioration of autoimmune cytopenias, or (4) development of adoptive allogeneic cellular immunotherapy and graft-versus-autoimmune effect [92].

There have been several reports of myeloablative AlloSCT performed in patients with malignant and nonmalignant diseases who had a concomitant autoimmune disease. Hinterberger et al. [93] previewed the data on patients who received AlloSCT for blood disorders (n = 30) with concomitant autoimmune disease. Nineteen who developed GVHD achieved remission. There are only a few case reports of successful RI AlloSCT in patients with autoimmune disorders (psoriasis and rheumatoid arthritis) [94,95]. The RI AlloSCT approach is appealing for refractory autoimmune diseases because of lesser transplant-related morbidity and mortality. Further studies are being conducted to define the role of RI AlloSCT for autoimmune disease. We have received an investigational new drug permit from the Food and Drug Administration (BB-IND 11093) to study RI AlloSCT for selected medically refractory autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic scleroderma, and juvenile idiopathic arthritis).

RI AlloSCT IN CHILDREN

Socié et al. [96] reported long-term survival and late effects after allogeneic bone marrow transplantation in 6691 patients who were free of their original disease for at least 2 years after AlloSCT. A large number of patients died of other secondary complications, including GVHD (31%), infection (6%), secondary malignancies (6%), and organ failure (6%). Children with nonmalignant disease who require myeloablative AlloSCT for curative intent face the above-mentioned long-term late complications associated with this therapy: the risks of growth failure, gonadal failure, secondary malignancies, and secondary MDS weigh heavily on the decision to proceed with curative-intent therapy. It remains to be determined whether a select group of children receiving RI conditioning therapy and AlloSCT will benefit from a reduced risk of disease recurrence and, at the same time, a reduced risk of long-term complications.

The historical experience of myeloablative AlloSCT in patients with sickle cell disease (SCD) or β-thalassemia major indicates that stable mixed hematopoietic chimerism may be sufficient to cure these hemoglobinopathies [97,98]. Thus, myeloablation per se may not be mandatory for the treatment of SCD, and this raises the possibility that RI conditioning regimens could be investigated as an alternative method to reduce long-term complications in this subpopulation. Studies in a murine model of SCD suggest that this approach could even be curative in the HLA-disparate setting [99]. Given the preliminary results of reduced acute toxicity after RI AlloSCT, this approach seems attractive for patients with SCD, particularly older patients and those with acquired organ toxicity, and it may offer children the potential to retain gonadal function and normal fertility. Iannone et al. [100], in a prospective multicenter study, described a nonmyeloablative SCT approach in 7 pediatric patients with SCD (n = 6) and thalassemia (n =1) who received pretransplantation fludarabine and 200 cGy of TBI with or without antithymocyte globulin. Regimen-related toxicity was minimal but resulted in only transient donor engraftment in 6 of 7 patients. These preliminary results suggest that more intensive conditioning is required for previously transfused patients with hemoglobinopathies than 2 Gy of total body irradiation and fludarabine (Table 6).

Mixed or complete donor chimerism achieved after RI AlloSCT can potentially alter the natural history and outcome of patients with nonmalignant diseases and spare them from short-term and possibly long-term toxicities. Amrolia et al. [101] used a nonmyeloablative approach with fludarabine, melphalan, and antithymocyte globulin for 2 patients with severe combined immunodeficiency disease and 6 patients with other immune deficiencies. Seven of 8 patients

Table 6. *RI AlloSCT in Children and Adolescents*

Study	n	Disease	Median Age, y (Range)	Donor	Regimen	Acute GVHD Prophylaxis	Myeloid and Platelet Recovery (Median Day)	Donor Chimerism* (% Patients)	Incidence of GVHD		Outcome
									Acute	Chronic	
Iannone [100]	7	Nonmalignant-7 (hemoglobinopathies)	9 (3–20)	MSD	Flu/LD-TBI/ATG	CSP + MMF Tacrolimus + MMF	5/0	57 (transient)	14%	0%	1-y OS-100%
Amrolia [101]	8	Nonmalignant-8	10 (0.75–18)	MRD MUD	Flu/Mel/ATG	CSP + steroids	13/22	100	50% (grade I)	10%	1-y OS-88%
Horwitz [102]	10	Nonmalignant-10	15 (5–36)	MRD	Flu/Cy/ATG	CSP	10/0	90	30%	10%	1-y OS-70%
Del Toro [104]	21	Malignant-13 Nonmalignant-8	13.5 (0.5–21)	MRD UCB	Flu based	Tacrolimus + MMF	16/21	91	38%	10%	1-y OS-60%
Jacobsohn [105]	13	Nonmalignant-10	5.2 (0.6–11)	MRD MUD UCB	Flu/Bu/ATG	CSP + MMF	18/14	54	8%	37%	1-y OS-84%
Gomez-Almaguer [106]	23	Malignant-15 Nonmalignant-8	13 (4–20)	MSD	Bu/Flu/Cy Flu, Mel	CSP + MTX	13/13	56	10%	13%	3-y OS-55%
Woolfrey [107]	15	Malignant-6 Nonmalignant-9	<21	MRD MUD	Flu/TBI TBI alone	CSP + MMF	NA	86	93%	80%	NA

MSD indicates matched sibling donors; MRD, matched related donors; MUD, matched unrelated donors; UCB, umbilical cord blood; Flu, fludarabine; LD, low dose; TBI, total body irradiation; ATG, antithymocyte globulin; Mel, melphalan; Cy, cyclophosphamide; Bu, busulfan; CSP, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; myeloid recovery, absolute neutrophil count >500/μL; platelet recovery, >20 000/μL; NA, not available; OS, overall survival.

*Any degree of donor chimerism.

were reported to survive from 8 to 17 months after RI AlloSCT (Table 6). The nonmyeloablative SCT approach permits rapid engraftment from sibling and unrelated donors with minimal toxicity, even in the presence of severe organ dysfunction, thus establishing host tolerance to the donor immune cells responsible for immune reconstitution. This regimen may prove useful for patients who are ineligible for conventional SCT. Long-term follow-up is needed before this approach is extended to patients at standard risk. Horwitz et al. [102] reported the results of a strategy that used a highly immunosuppressive but nonmyeloablative regimen in 10 patients with chronic granulomatous disease and a history of life-threatening infections. Donor chimerism was established in 9 of the 10 patients, and 8 patients had circulating oxidase-positive phagocytes at follow-up (Table 6). The question of whether a 30% mortality rate is acceptable must be asked. With the advent of modern antimicrobial prophylaxis and treatment, these children are thriving [103], and more aggressive treatments, such as bone marrow transplantation, are debatable in this disease.

We recently reported the preliminary results in 21 children who received RI AlloSCT [104]. Our study population included 14 patients with malignant and 7 patients with nonmalignant disease who were conditioned with fludarabine-based regimens. Sixteen of 21 patients showed evidence of myeloid engraftment. Three primary and 2 secondary graft failures occurred in patients with β-thalassemia, hemophagocytic lymphohistiocytoses, MDS, and severe aplastic anemia. The 1-year OS for good-risk versus poor-risk patients (International Bone Marrow Transplantation Registry criteria) was 88.9% versus 38.9%, respectively. These results, however, include a heterogenous group of patients with different donor sources and different RI conditioning regimens. These preliminary results should be interpreted with caution until larger groups of children with a homogenous diagnosis, cell source, and RI regimen are used. It remains to be determined what degree of intensity is required for different pediatric subpopulations. Patients with primary refractory hematologic disease, including hemoglobinopathies, MDS, hemophagocytic lymphohistiocytoses, or severe aplastic anemia, may require more intense nonmyeloablative conditioning and immunosuppression to prevent graft rejection. Also, the small dose of stem cells in cord blood units might be a factor in graft rejection, and combining cord blood units might improve engraftment. Because transplant-related morbidity after RI AlloSCT is low, in these patients with graft failure, a second AlloSCT with a myeloablative regimen may be feasible. To accurately determine the difference, if any, of late long-term effects in pediatric recipients after RI AlloSCT, studies in selected patient populations with much longer follow-up are required.

Results from other pediatric studies [105-107] are reported in Table 6.

INFECTIOUS COMPLICATIONS AFTER RI AlloSCT

The potential mechanisms of reduced infectious morbidity after RI AlloSCT include decreased duration of severe neutropenia, reduced grade of mucositis, enhanced immune reconstitution, and decreased rates of severe acute GVHD [108,109]. Data on infections in nonmyeloablative SCT recipients are preliminary, and differences in the degrees of myeloablation may lead to considerable variation in outcomes. Junghanss et al. [110] reported the results of a matched pair analysis of 56 RI AlloSCT recipients and compared the rates of various infections with 112 controls who had received myeloablative AlloSCT. Bacterial infections during the first 30 days, however, were significantly reduced in RI AlloSCT recipients (9% versus 27%; $P = .01$), with a trend toward a reduction during the first 100 days after RI AlloSCT (27% versus 41%; $P = .07$). In a subgroup analysis, infections commonly observed during periods of mucositis (gram-negative bacteria, streptococci, and enterococci) were significantly fewer in RI AlloSCT recipients. In the same matched cohort study [110], RI AlloSCT recipients seemed to have equivalent risks for aspergillosis compared with recipients after myeloablative AlloSCT (15% versus 9%; median follow-up, 12.7 months). There seems to be a trend, however, toward an increased 1-year survival after aspergillosis in RI AlloSCT recipients (63%). Identified risk factors for developing cytomegalovirus (CMV) disease include lymphopenia and the CMV serologic status of the donor and recipients [111,112]. Junghanss et al. [110] reported that CMV-positive recipients of RI AlloSCT showed trends toward a lower incidence of CMV antigenemia, CMV viremia, and CMV disease during the first 100 days after transplantation compared with the myeloablative AlloSCT group and that CMV disease occurred significantly later among RI AlloSCT patients. Use of alemtuzumab for immunosuppression before RI conditioning can also increase the risk of CMV infection. Chakrabarti et al. [113] reported a 50% incidence of CMV infection at a median of 27 days after nonmyeloablative SCT with a probability of 84.8% in patients at risk of CMV infection. The results of the infectious disease reported from small studies should be verified in multiple larger studies, especially considering the substantial variation between conditioning regimens. This information will be critically important to guide the development of rational preventative strategies in RI AlloSCT recipients.

ACUTE GVHD AFTER RI AlloSCT

The immune reconstitution after RI AlloSCT differs from myeloablative SCT in several important aspects. First, RI AlloSCT conditioning seems to cause only limited tissue damage. Second, development of transient mixed donor-host chimerism may facilitate establishment of mutual tolerance, which, in turn, may downregulate GVH activity [23,24]. Third, the type and duration of immunosuppressive agents administered after RI AlloSCT conditioning may sufficiently differ from those used after myeloablative AlloSCT [108,109,114]. Fourth, the number and function of recipient antigen-presenting cells (APCs) may be higher after RI AlloSCT as compared with myeloablative AlloSCT. These cells may play a major role in the initiation of GVH responses early after SCT [115,116]. The net clinical effects of these fundamental differences between nonablative and myeloablative allogeneic conditioning regimens on the incidence or severity of GVHD remain to be defined. Mielcarek et al. [117] retrospectively analyzed data from 2 age-matched cohorts of patients who had received either nonablative or myeloablative AlloSCT from HLA-matched related and unrelated donors. The cumulative incidence of grade II to IV acute GVHD at day +100 after matched related donor allografting was significantly lower among RI AlloSCT recipients than among myeloablative recipients ($P = .02$), but there was no difference in the cumulative incidences of grade III or IV acute GVHD or extensive chronic GVHD between the 2 groups. After unrelated donor allografting, the cumulative incidences of both grades II to IV and grades III and IV acute GVHD at day +100 were lower among RI AlloSCT recipients than among myeloablative transplant recipients ($P = .01$; Figure 5), but the cumulative incidence of extensive chronic GVHD was not significantly different. The cumulative incidence rates of death with manifestations of GVHD during treatment were 35% and 24% at 15 months for the myeloablative and RI AlloSCT groups, respectively ($P = .27$); deaths tended to occur later in the RI AlloSCT group.

CHRONIC GVHD AFTER RI AlloSCT

Because the length of follow-up is relatively short, it is difficult to accurately assess the incidence and severity of chronic GVHD after RI AlloSCT. However, studies from many centers [20,118,119] have reported that the incidence of extensive chronic GVHD is at least comparable or higher for patients who undergo nonmyeloablative regimens as compared with conventional myeloablative allografting. Several factors seem to predispose nonmyeloablative recipients to be at increased risk for chronic GVHD. First, the population that receives these less toxic regimens

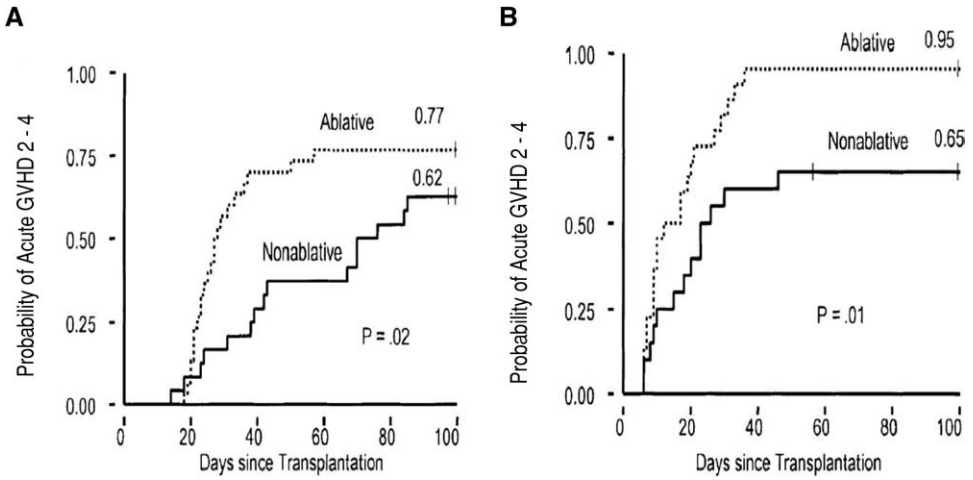

Figure 5. Cumulative incidences of acute GVHD after nonmyeloablative conditioning compared with myeloablative conditioning. A, Related donor transplantation. B, Unrelated donor transplantation. Reprinted with permission from the American Society of Hematology [117].

is generally older, and older age is more permissive for development of chronic GVHD. A second factor is that PBSCs, as compared with bone marrow, are the preferred graft source. Studies comparing the outcome of myeloablated recipients who received PBSC transplants versus bone marrow demonstrated consistent trends toward higher cumulative incidences of chronic GVHD in recipients of PBSCs [120-122]. Peripheral blood is the preferred graft source for nonmyeloablative transplantations because it contains significantly more hematopoietic stem and progenitor cells. Both of these cell populations are required to achieve durable and robust allogeneic hematopoietic cell engraftment. Graft content is particularly important for nonmyeloablative regimens because higher resistance to engraftment is encountered. As compared with myeloablated recipients, nonmyeloablated patients retain more recipient hematopoietic and lymphoid elements, both of which contribute significantly to resistance to engraftment. A third reason that chronic GVHD may become more prevalent in nonmyeloablated recipients is due to the use of DLI. Because RI AlloSCT principally relies on GVT activity to control malignancies, DLI is one of the first therapeutic maneuvers considered when a stably engrafted patient has evidence of disease persistence, progression, or relapse. A prior clinical study examining 140 patients who relapsed after AlloSCT showed that chronic GVHD developed in roughly 60% of patients who underwent DLI as salvage treatment [10]. Perhaps of greater significance is the observation that chronic GVHD occurred in >80% of DLI patients who responded to treatment [10]. A fourth potential and as yet unexplored variable is the effect that residual host populations have on GVHD pathogenesis. As compared with conventional myeloablative regimens, nonmyeloablative conditioning spares more recipient immune cells. Cellular interactions that are likely to be affected by these differences include donor and surviving host T lymphocytes with APCs and lymphocyte regulatory circuits. Studies in mice suggest that such a recipient population induces a pathogenic response, because elimination of host APCs, host $CD4^+$ cells, or both abrogates the development of GVHD [115,123]. A fifth potential variable is that the tolerance induced by mixed chimera may reduce chronic GVHD, and, finally, the incidence of chronic GVHD may vary between different RI regimens because of the difference in kinetics of engraftment. Better understanding and further development of immunosuppressive drugs might result in better treatment of GVHD. This in turn could lead to the more widespread use of RI AlloSCT for the treatment of patients with malignant and nonmalignant diseases.

IMMUNE RECONSTITUTION AND BIOLOGICAL CORRELATES OF ENGRAFTMENT AFTER RI AlloSCT

The immune system of patients after myeloablative AlloSCT is characterized by impaired immunologic responses to recall antigens as well as to mitogenic or allogeneic stimuli, and this predisposes them to various infections. Morecki et al. [124] demonstrated that patients who received RI AlloSCT featured early recovery of the T cell–dependent mitogenic response and non–major histocompatibility complex–restricted cytotoxicity when compared with myeloablative AlloSCT. Similarly, Mohty et al. [125] demonstrated an early recovery of leukocytes, $CD8^+$, NK lymphocytes, and circulating dendritic cells. However, in both of these studies, the number of patients was small, and immune reconstitution was compared with that of historical controls. Randomized studies can answer whether early immune recovery can translate into a decrease in the risk of infec-

tion. Moreover, in most of the studies shown in Tables 1 to 6, myeloid and platelet engraftment is faster than conventional myeloablative SCT to the extent that some patients do not have a nadir absolute neutrophil count <500/μL or a platelet count <20 000/μL. Faster myeloid and platelet engraftment may result in a decreased incidence of mucositis and febrile neutropenia and also a decrease in use of blood products and length of hospital stay [34]. Many centers are now performing RI AlloSCT in the outpatient setting [34,126].

Monitoring the levels of donor chimerism among the peripheral blood cell subpopulation after RI AlloSCT might help identify patients at risk for graft rejection, acute GVHD, and relapse. Only a few reports to date have analyzed the engraftment kinetics of specific hematopoietic lineages after RI AlloSCT and evaluated the effect of the kinetics and degree of donor chimerism on outcome. Childs et al. [127] studied chimerism evolution in 15 patients conditioned with cyclophosphamide and fludarabine. Full donor chimerism was achieved earlier among T cells than among granulocytes, and the progression to full donor T-cell chimerism preceded GVHD and antitumor responses. Baron et al. [128] recently reported that earlier establishment of donor NK cell chimerism was associated with improved progression-free survival.

FUTURE DIRECTIONS AND CHALLENGES

Although RI AlloSCT alone is unlikely to cure most patients with metastatic solid tumors, these pilot studies have been invaluable because they have provided important proof of concept of the therapeutic potential of the GVT effect. On the basis of these observations, second-generation regimens that incorporate strategies to cytoreduce tumors before transplantation (eg, autologous transplantation followed by RI AlloSCT, surgical or chemotherapeutic debulking, or targeted small molecules) and methods to target the donor immune system will likely be forthcoming. Increased understanding of tissue-specific polymorphic minor histocompatibility antigens might lead to the development of vaccines that could be used to direct the donor cytotoxic T cells toward tumor targets rather than the typical tissues involved in GVHD. Targets include antigens present on both malignant and nonmalignant marrow cells and possibly even polymorphic antigens present on certain metastatic solid tumors.

Many issues remain to be addressed regarding how to perform RI AlloSCT for various hematologic and nonhematologic malignancies. Conditioning regimens used in different studies vary from minimally ablative (low-dose total body irradiation) to almost myeloablative. Randomized studies should be performed to compare various regimens and pretransplantation immunosuppression for specific malignant and nonmalignant diseases. Similarly, there is a need to report engraftment status and donor chimerism in a uniform fashion so that meaningful comparisons can be made. Measuring the levels of peripheral blood NK cell subset donor chimerism may provide useful information on RI AlloSCT outcomes and might allow early therapeutic interventions to prevent graft rejection or disease progression. After RI AlloSCT, serial characterization of donor chimerism might offer the possibility of identifying patients who are at the highest risk of developing relapse and who can be rescued by immunotherapy.

Regardless of the technical approaches to RI AlloSCT, there is a fundamental requirement that controlled clinical trials be performed with well-defined hematologic and nonhematologic malignancies to evaluate the role of RI AlloSCT more fully. Although most patients reported so far were heavily pretreated and often had chemoresistant disease, these patients may not be ideal for controlled trials because of the lack of alternative therapies. More appropriate would be the patients with hematologic and nonhematologic malignancies who have experienced treatment failure with initial therapies, who have a poor prognosis, and for whom salvage therapies exist that might be used for comparison against RI AlloSCT. Finally, curative treatment modalities work best when used early in the disease course, and this strategy likely will also apply to RI AlloSCT. This consideration must be balanced by the fact that treatment-related mortality with RI AlloSCT is significant and exceeds that of other frequently used therapies. One might anticipate that technical refinements and use in patients with earlier-stage disease will enhance the safety of RI AlloSCT and thus increase acceptance of this modality for future clinical trials. There has been a proliferation of reports of RI AlloSCT in both adults and, more recently, children with both malignant and nonmalignant disease in phase I and phase II pilot studies. We are now at the end of the beginning of RI AlloSCT as a therapeutic modality, and the future should be more focused with hypothesis-driven translational studies to promote an increased understanding of the full potential of this therapeutic concept.

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